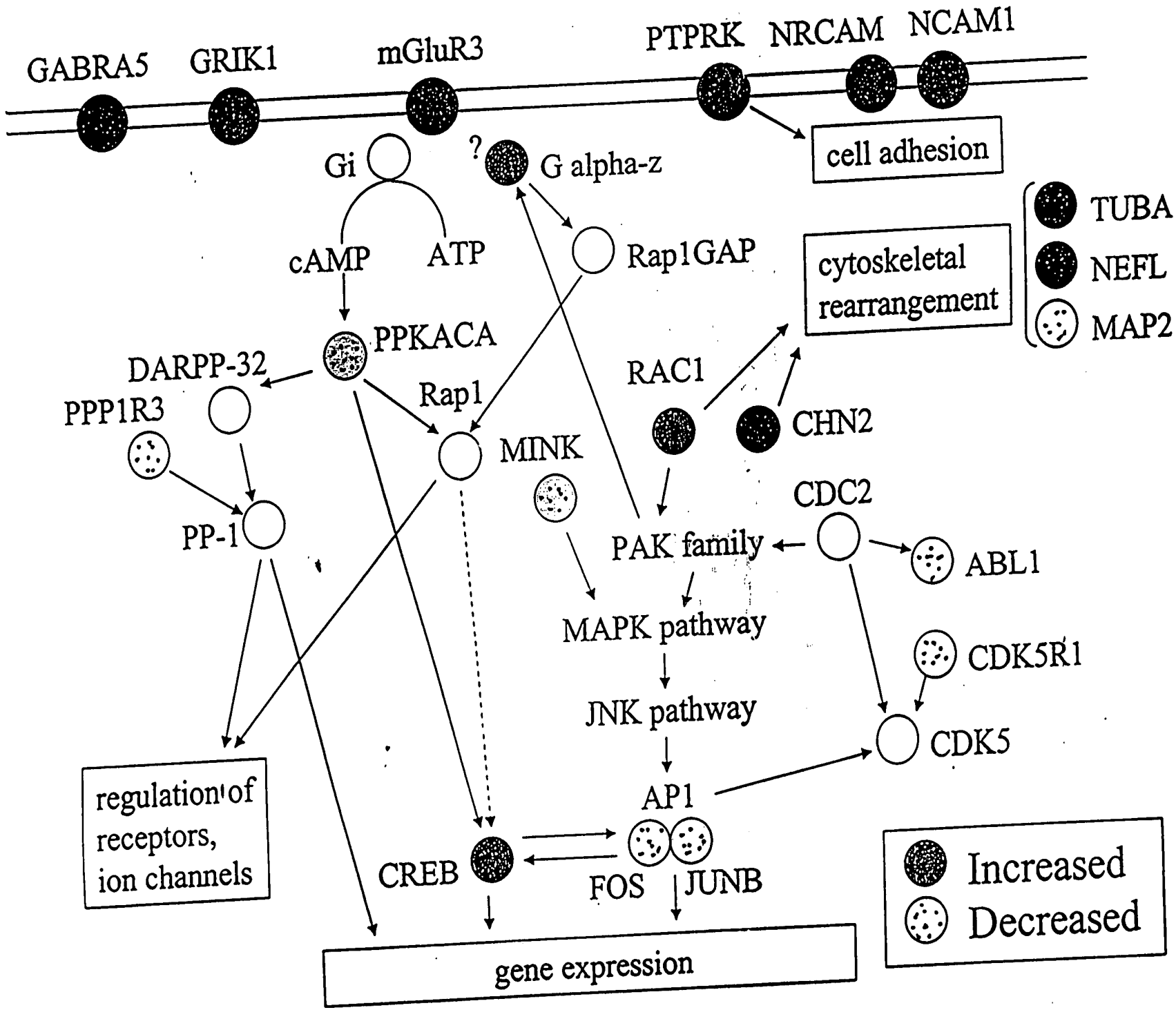

GABRA5
GRIK1
mGluR3
PTPRK
NRCAM
NCAM1
cell adhesion
Gi
?
G alpha-z
cAMP
ATP
Rap1GAP
cytoskeletal rearrangement
TUBA
NEFL
MAP2
PPKACA
DARPP-32
PPP1R3
Rap1
RAC1
CHN2
MINK
CDC2
PP-1
PAK family
ABL1
MAPK pathway
CDK5R1
JNK pathway
CDK5
AP1
regulation of receptors, ion channels
CREB
FOS
JUNB
Increased
Decreased
gene expression

Figure 1

Summary of Functions for Signal Transduction Transcripts Differentially Expressed in MDD

- **GRB2 (growth receptor binding protein 2).** An adaptor protein that transduces signal from an activated growth factor receptor, culminating in the activation of Ras.
- **ITPKB (inositol-1,4,5-triphosphate-3 kinase B).** A member of a family of kinases involved in inositol triphosphate signal transduction.
- **PAK-1 (p21 activated kinase 1).** A protein that is regulated by small-GTP binding proteins, like Ras, and is believed to directly act on the JNK1/MAP kinase signal transduction cascade.
- **PKC, beta1 (protein kinase C, beta 1).** A protein kinase involved in several Ca^{++} and IP_3 dependent signal transduction cascades.
- **RalGDS (Ral guanine nucleotide dissociation stimulator).** Stimulates dissociation of GDP from Ras and Ras-like (Ral) small G-proteins, thereby, increasing the rate of GTP-GDP exchange and facilitating activation of Ras/Ral proteins.
- **RAP1 (GTPase activating protein 1).** Stimulates GTPase activity of small GTP-binding proteins, thereby terminating their activity and functionally inhibiting Ras/Ral proteins.
- **RGS20 (regulator of G-protein signaling 20).** A GTPase activating protein that has specificity for the alpha z subunit of heterotrimeric G-proteins. Facilitation of GTPase activity would terminate signal transduction and thus act as a negative regulator.

Figure 2

bFGF System Transcripts are Differentiall Expressed in PFC in Subjects with MDD

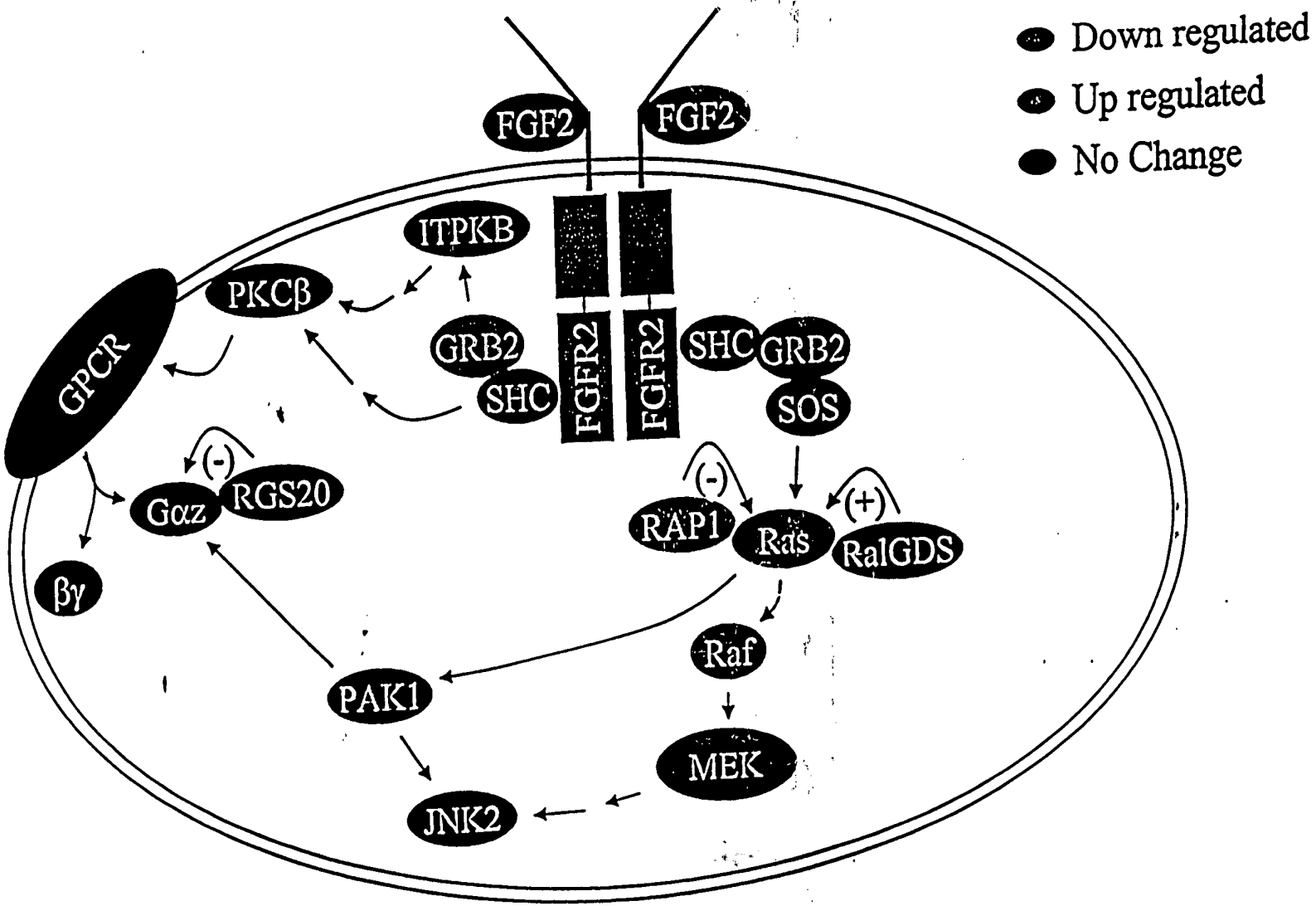


Figure 3

Fold Change and p-values for bFGF system Transcripts in PFC for MDD Subjects

probe set ID	Gene	Accession #	Fold Change	p-value
1593_at	FGF2	J04513	-1.4	0.04
1363_at	FGFR2	M87770	-1.4	0.02
1143_s_at	FGFR2	M87771	-1.2	0.04
33855_at	GRB2	M96995	1.2	0.06
37272_at	ITPKB	X57206	-1.4	0.05
1557_at	PAK1	U24152	-1.4	0.01
1558_g_at	PAK-1	U24152	1.6	0.05
1217_g_at	PKC beta 1	X07109	-1.6	0.02
36550_at	RalGDS	AL049538	-1.5	0.01
1270_at	RAP1	M64788	1.2	0.06
41086_at	RGS 20	AF060877	-1.6	0.04

Figure 4

Figure 5

Metabolic pathways significantly dysregulated

Pathway	GS/GOC	posibility of false positive
oxidative phosphorylation	8/95	0.0017
terpenoid biosynthesis	2/5	0.0057
proteasome	3/30	0.0360
ATP synthesis	3/32	0.0425
sterol, vitamin K/E, carotenoid biosynthesis	2/17	0.0643
Parkinson's disease	2/21	0.0934
sphingophospholipid	1/4	0.0955
nitrogen metabolism	2/23	0.1091
galactose metabolism	2/24	0.1172
glutathion metabolism	2/32	0.1866
glycine, serine, threonine methabolism	2/33	0.1957

GS/GOC; genes selected/genes on a chip

Figure 6

Signaling & Metabolic Pathways Significantly Altered in AnCg of Bipolar Subjects

1.	Inositol Phosphate Metabolism	14/135
2.	Nicotinate and Nicotimade Metabolism	11/116
3.	Benzoate Degradation N-Ac CoA Ligation	11/118
4.	Alanine and Aspartate Metabolism	4/18
5.	Starch and Sucrose Metabolism	11/132
6.	Sphingoglycolipid Metabolism	11/134
7.	Glutamate Metabolism	4/21
8.	Phosphotydil-Isositol Signaling	8/101

Figure 7

Three Over Expressed Genes Are Located in the Same Chromosomal Region

Symbol	Description	Cytogenetic Band (Mb)
SGNE1	Secretory granule, neuroendocrine protein 1 (7B2 protein)	15q13
NDN	Necdin homolog (mouse)	15q11.2
GABRA5	Gamma-aminobutyric acid (GABA) A receptor, alpha 5	15q11.2

Figure 8

Three of the 13 genes are on 15q11-13 within the Prader Willi region (SGNE1, GABRA5, and NDN)

symbol	orient.	links	evidence	cyto.	full name
MAGEL2	↑	sv ev hm seq mm	C	15q11-q12	MAGE-like 2
NDN	↑	sv ev hm seq mm	C	15q11.2-q12	necdin homolog (mouse)
UBE3A	↑	sv ev hm seq mm	C	15q11-q13	ubiquitin protein ligase E3A (h
GABRA5	↓	sv ev hm seq mm	C	15q11.2-q12	gamma-aminobutyric acid (G/
OCA2	↑	sv ev hm seq mm	C	15q11.2-q12	oculocutaneous albinism II (pi
RPL41P2	↓	sv ev - seq mm		15q11-q13	ribosomal protein L41, pseud
KIAA0574	↑	sv ev - seq mm	C	15q12	KIAA0574 protein
HCA4	↑	sv ev - seq mm	C	15q12	hepatocellular carcinoma-asso
CHRFAM7A	↑	sv ev - seq mm	C	15q14	CHRNA7 (cholinergic recept
DKFZP434L187	↓	sv ev - seq mm	C	15q13.1	DKFZP434L187 protein
LOC161725	↓	sv ev - seq mm	C	15q12	cezanne 2
KLF13	↑	sv ev hm seq mm	C	15q12	Kruppel-like factor 13
MN7	↓	sv ev - seq mm	C	15q11-q13	D15F37 (pseudogene)
SGNE1	↓	sv ev hm seq mm	?	15q13-q14	secretory granule, neuroendoc
LOC51234	↓	sv ev hm seq mm	C	15q13.1	hypothetical protein LOC512
GOLGIN-67	↑	sv ev - seq mm	C	15q11.2	golgin-67

These 3 genes are found within a 7 Mb region that contains 10 other genes.

Figure 9

Genes Regulated in Human Postmortem Tissue (Dorsolateral PFC and Anterior Cingulate)

Gene	MDD DLPC	MDD AnCg	BD DLPC	BD AnCg
neuronal cell adhesion molecule	↑			
solute carrier family 14 (urea transporter) member	↓			
protein kinase C, beta 1	↑	↑		
NEL-like 1	↑			
phosphoribosyl pyrophosphate synthetase	↑			
solute carrier family 1 (glial high affinity glutamate transporter) member		↓		
glutamate receptor, metabotropic 3				↑
Microtubule Associated Protein 2			↑	
Fribroblast Growth Factor 2		↓		
GABA A Receptor				↑
Inositol 1,4,5-triphosphate receptor		↑		

GPCR and cAMP/PI/Rho pathways

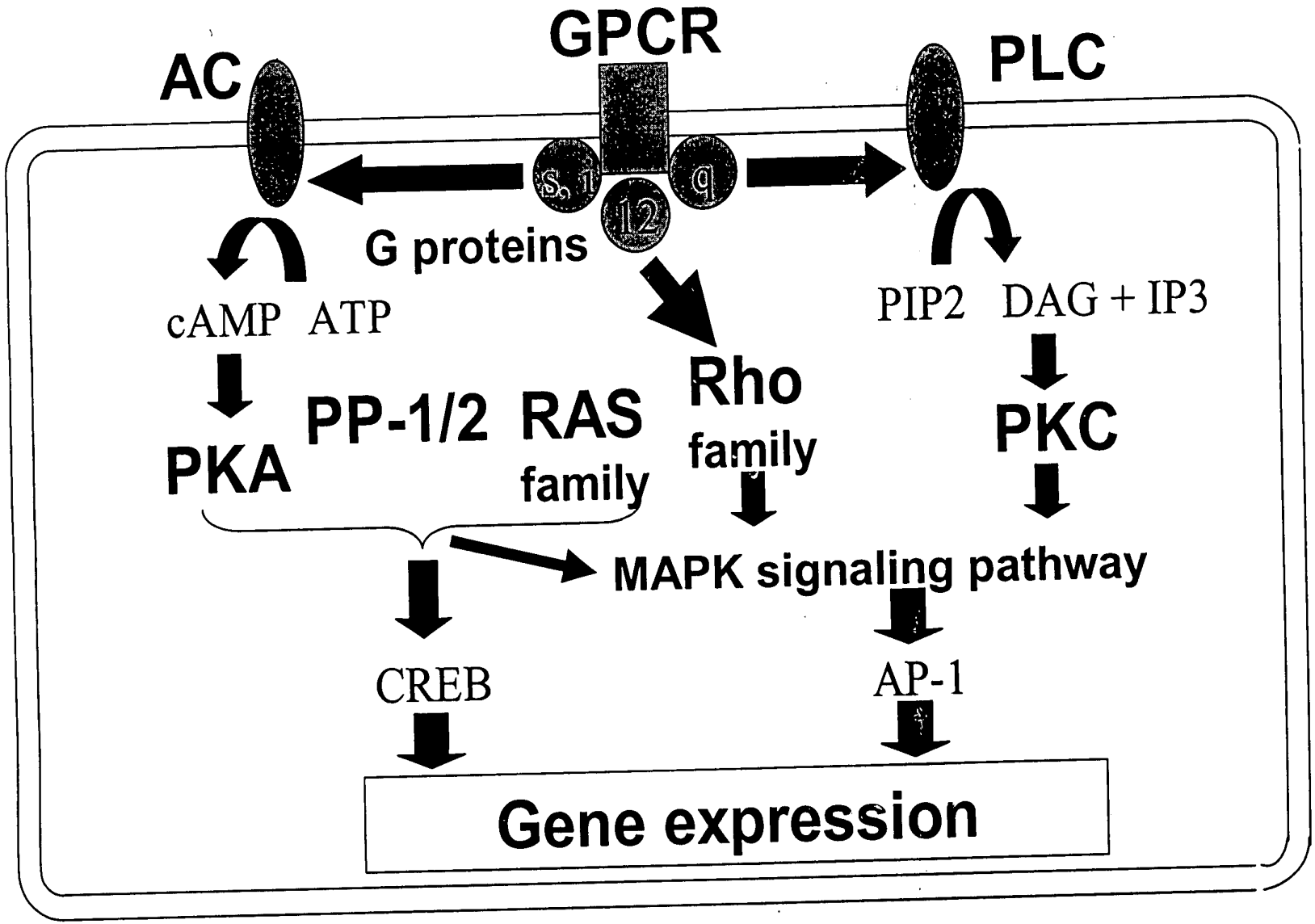


Fig. 10

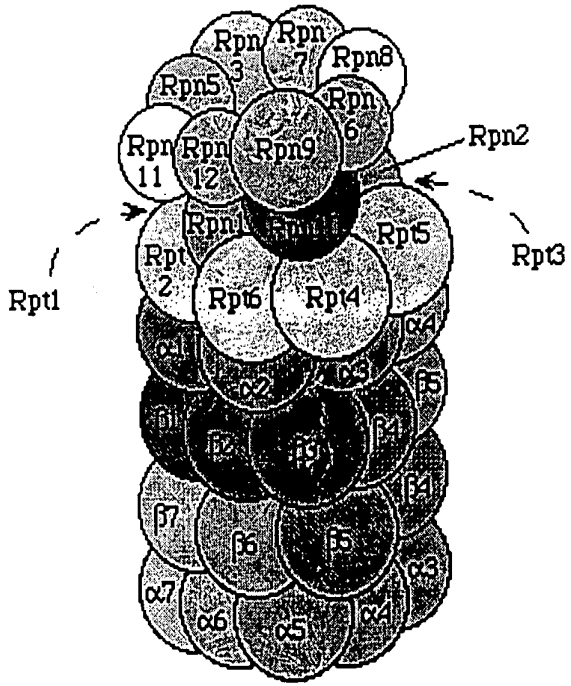
Proteasome: Alterations in In Bipolar Ss, Anterior Cingulate

-28 subunits
-Four rings of seven.
-Outer rings: alpha subunits
-Inner Rings: beta subunits
-Beta: responsible for peptidase activity.
-Degrades Short-lived and Misfolded Proteins
-Role in Ubiquitination
-ATP Dependent Activity

Note: 11 / 31 genes are significant, mostly Beta

Fig. 11

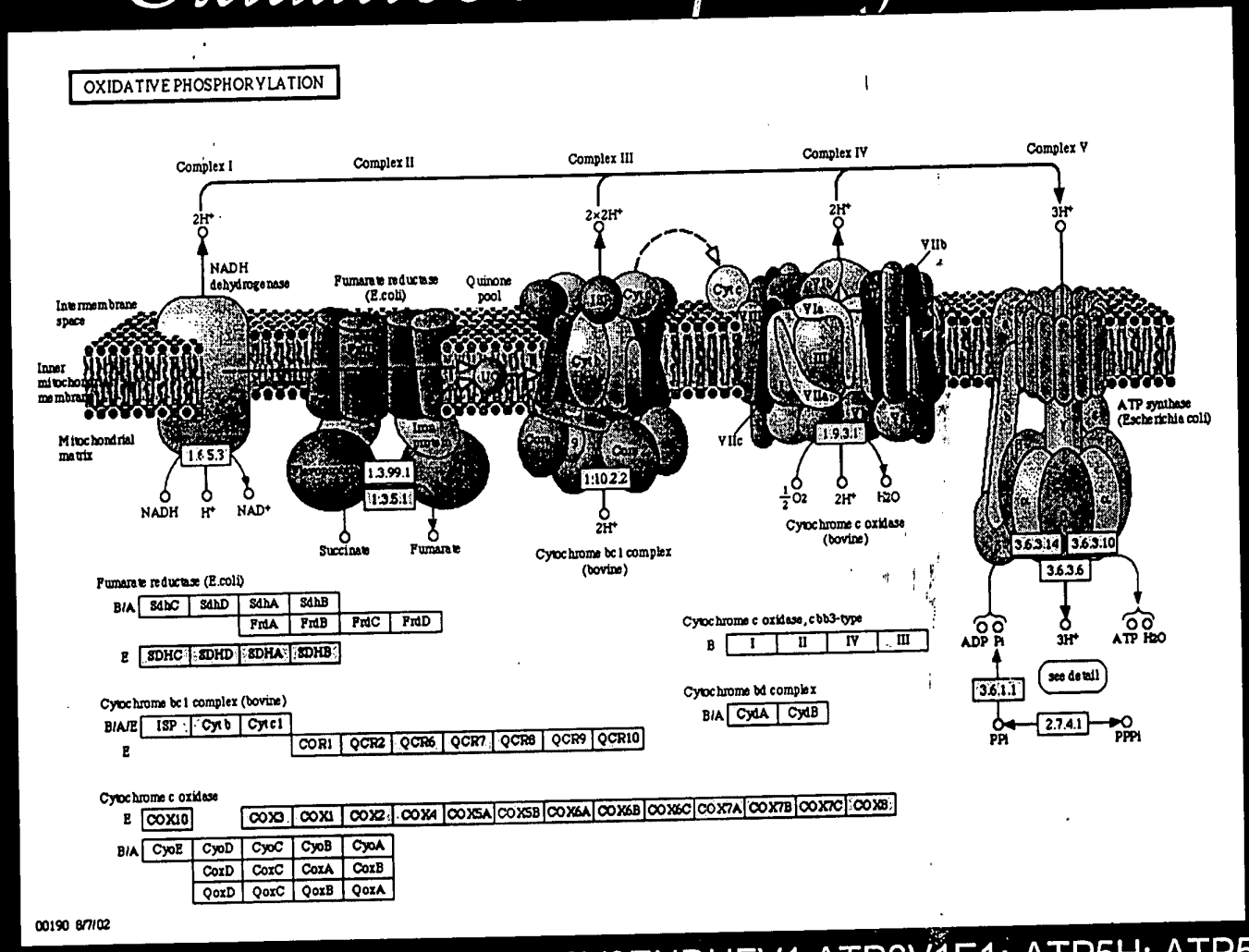
PROTEASOME



26S Proteasome (Saccharomyces cerevisiae)

Rpn1	Rpn2	Rpn3	Rpn4	Rpn5	Rpn6	
Rpn7	Rpn8	Rpn9	Rpn10	Rpn11	Rpn12	
Rpt1	Rpt2	Rpt3	Rpt4	Rpt5	Rpt6	
α1	α2	α3	α4	α5	α6	α7
β1	β2	β3	β4	β5	β6	β7

Oxidative Phosphorylation



- ATP5A1; ATP6V1A1; ATP6V0E; ATP6V0ENDUFV1;ATP6V1E1; ATP5H; ATP5J; ATP6V0B; ATP5O;ATP5J2; ATP6V0D1
- NDUFS7; NDUFB5;NDUFS2; NDUFC1;NDUFB3
- COX7B; SDHB; UQCRC2

Fig. 12

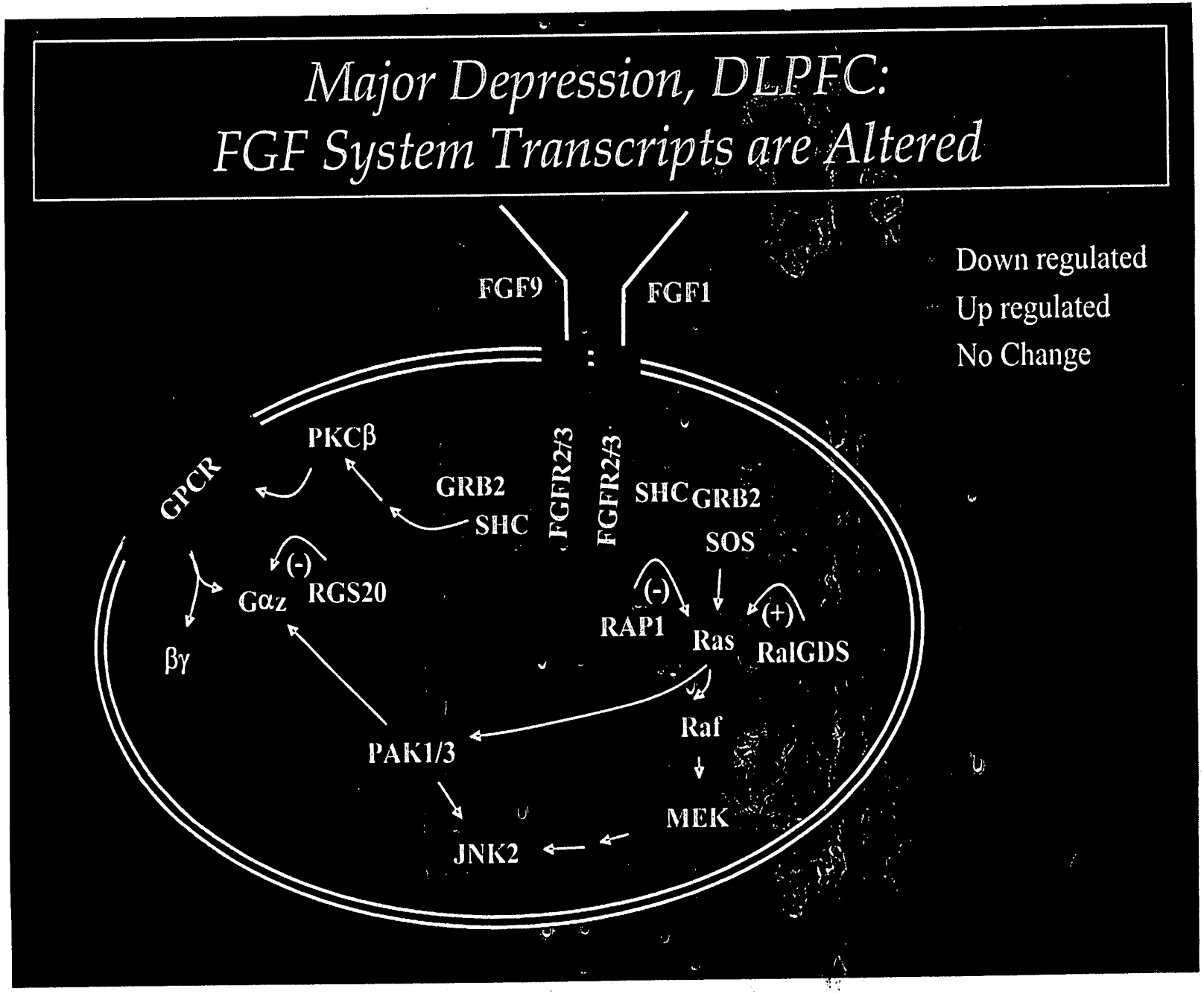

Major Depression, DLPFC:
FGF System Transcripts are Altered
Down regulated
Up regulated
No Change
FGF9
FGF1
PKCβ
GPCR
GRB2
SHC
FGFR2/3
FGFR2/3
SHC
GRB2
SOS
(-)
Gαz
RGS20
βγ
(-)
RAP1
Ras
(+)
RalGDS
Raf
PAK1/3
MEK
JNK2

Fig. 13

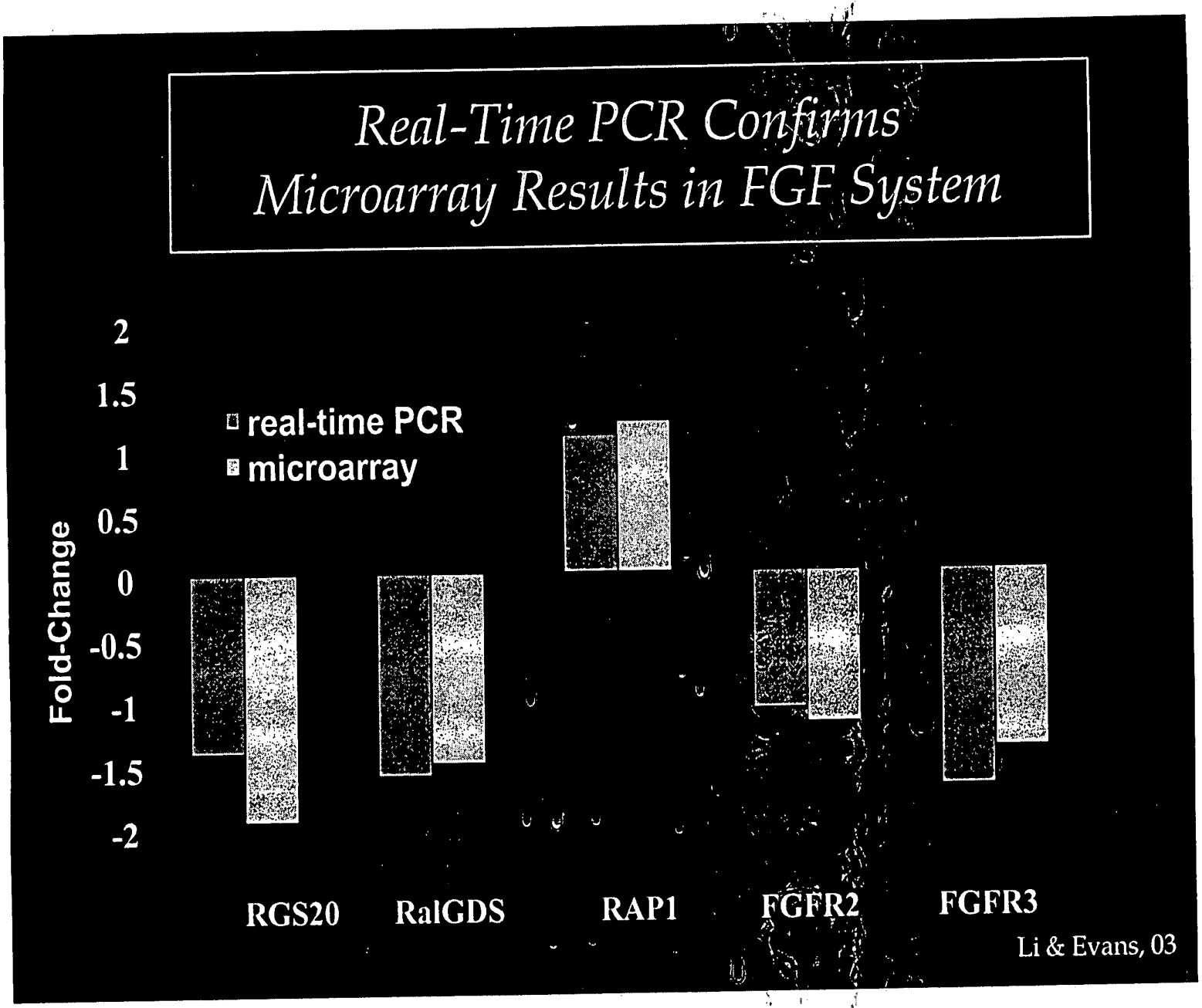

Real-Time PCR Confirms Microarray Results in FGF System
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
Fold-Change
real-time PCR
microarray
RGS20
RalGDS
RAP1
FGFR2
FGFR3
Li & Evans, 03

Fig. 14

Signaling Pathways involving GABA & Glutamate

BPD_AnCg

- GABRA5 — GABA A Receptor, alpha 5
- GRIA1 — Glut Receptor, ionotropic, AMPA1
- GRM3 — Glut Receptor, metabotropic 3
- GRIA3 — Glut Receptor, ionotropic, AMPA3
- GRIK1 — Glut Receptor, ionotropic, kainate1

BPD_DLPFC

- GABRA5 — GABA A Receptor, alpha 5
- GABBR1 — GABA B Receptor 1
- GABARAPL2 — GABA (A) Receptor-assoc. protein-like 2
- **(None Down)**

MDD_AnCg

- **(None UP)**
- SLC1A3 — Solute carrier family 1 (glial high affinity glut transporter), member 3
- SLC1A2 — Solute carrier family 1 (glial high affinity glut transporter), member 2
- GLUL — Glutamate-ammonia ligase (glutamine synthase)

MDD_DLPFC

- GABARB2 — GABA A receptor, beta 3
- GABARG2 — GABA A receptor, gamma 2
- GRIA1 — Glut Receptor, ionotropic, AMPA1
- GRIK5 — Glut Receptor, ionotropic, kainite 5
- SLC1A3 — Solute carrier family 1 (glial high affinity glut transporter), member 3
- SLC1A2 — Solute carrier family 1 (glial high affinity glut transporter), member 2
- GLUL — Glutamate-ammonia ligase (glutamine synthase)

Black: Up-regulated; Red: Down-regulated

Fig. 15